09/054,847 claim	08/571,755 claim	Corresponding CIP claim
	65 Rejected	10
	66 Rejected	11
	67 Rejected	12
	69 Free of prior art	13 Free of prior art
	70 Free of prior art	14 Free of prior art
	71 Free of prior art	15 Free of prior art
	72 Free of prior art	16 Free of prior art
	73 Free of prior art	17 Free of prior art
	74 Free of prior art	18 Free of prior art
	75 Free of prior art	19 Free of prior art
	76 Free of prior art	20 Free of prior art
	77 Free of prior art	21 Free of prior art
	78 Free of prior art	22 Free of prior art
	79 Free of prior art	23 Free of prior art
16 Rejected		24
17 Rejected		25
18 Rejected		26
19 Rejected		27
20 Rejected		28
21 Rejected		29
22 Rejected		30
23 Rejected		31
24 Rejected		32
25 Rejected		33
30 Rejected		34
31 Rejected		35
32 Rejected		36
33 Rejected		37
34 Rejected		38
54 Rejected		39

As indicated, the subject matter of claims 6-9 and 13-23 (corresponding to claims 58-61 and 69-79 of the 08/571,755 application) is free of prior art.

II. Patentability Arguments

i. U.S. Application No. 09/054,847

Claims 24-39 of the present application correspond to claims 16-25, 30-34 and 54 of the 09/054,847 application, which were rejected variously under 35 U.S.C. § 103(a) as allegedly being unpatentable over Griffiths (n13) in view of Lucas (C57), Dasch (a13), Derynck (u17) and Danielpour, and further in view of Presta (b13), Morgan (c13) or Braun (d13). By way of summary, the Examiner alleged that the cited references necessarily possess the inherent features which are recited in the present claims.

The applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. § 103(a) for at least two reasons. It is noted that the rejection in the 09/054,847 application under 35 U.S.C. § 103(a) is based on inherency. However, inherency cannot properly provide the basis for a rejection under 35 U.S.C. § 103(a). Jones v. Hardy, 230 USPQ 1021, 1025 (Fed. Cir. 1984) (*Consideration of an inherent quality is relevant only to anticipation, not obviousness.*)

The Examiner has failed to point out that in addition to the claimed binding characteristics of the claimed antigen binding domains, which are not taught or suggested by the cited art nor are they inherent to any antibody that binds to TGFβ1, the present claims also recite specific sequences not taught or suggested by the prior art. More specifically, the Examiner has failed to indicate how the recited sequences are inherent to the prior art or how such sequences could have been suggested by the prior art.

In view of the failure of the art to suggest such sequences, the applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. § 103(a).

The Examiner also maintains the position that molecules in the cited art that comprise an antigen binding domain specific for TGFβ1 inherently possess the characteristics of the claimed first specific binding member. The Examiner indicated that this rejection could be "rebutted by evidence showing that the products do not necessarily possess the characteristics of the claimed product." (Office Action, paper 27, page 3, end of first paragraph).

The Applicants submit that there is clear evidence in the cited art itself that the antibodies have binding characteristics that differ from one another, *e.g.*, do not all bind the same epitope or target molecule, and therefore do not necessarily possess the characteristics of the claimed product.

Lucas teaches three mouse monoclonal antibodies that bind TGFβ1. Table II of that document shows the results of cross blocking experiments which indicate the ability of each antibody to block the binding of the other antibodies. Antibodies designated as "4A11" and "2G7" are shown to bind to "distinct but closely related" epitopes and each inhibits the binding of the other. The third antibody, designated 12H5, however, shows little blocking of the other monoclonal antibodies and appears to bind to a "distinct" epitope of TGFβ1. All three monoclonal antibodies are

also shown to possess different neutralization activities (Table I). In particular, the antibody designated as "4A11" only neutralizes TGFβ1 whereas the antibody designated as "2G7"neutralizes TGFβ2 and TGFβ3 as well as TGFβ1. Thus, all three monoclonal antibodies of Lucas bind to distinct epitopes and have distinct binding properties, therefore, suggesting that any given antibody to a given target does not inherently possess the same binding properties of any other antibody that binds to that target.

Dasch et al. teaches four monoclonal antibodies which bind TGFβ2. Only one of these antibodies (1D11.16) binds TGFβ1 or has neutralization activity. Furthermore, only one of these antibodies, 2G1.1.12, binds to reduced monomeric TGFβ2. Figure 4 of Dasch et al. indicates that all four antibodies precipitate iodinated TGFβ2 to different extents. Thus, even in the absence of specific cross-blocking data, it is evident that all four monoclonal antibodies have distinct binding properties even though they bind to the same target molecule. It is also evident; of course, that antibodies which do not bind TGFβ1 will not bind TGFβ1 preferentially over TGFβ3, as is presently claimed.

It is noted that inherency may not be established by probabilities or possibilities regarding what may have resulted in the prior art. *In re Oelrich*, 666 F.2d 578, 212 USPQ 323, 326 (CCPA 1981). Because of the variation in binding properties of antibodies to the same target molecule as illustrated by the cited art, the prior art products cannot properly be presumed to inherently possess properties of the presently claimed antibodies. On that basis, the applicants submit that the present claims meet the requirements of 35 U.S.C.§ 103(a).

ii. <u>U.S. Application No. 08/571,755</u>

The Examiner of 08/571,755 maintained the rejection of claims 51-54 (now claims 1-5) under 35 U.S.C. (a) as allegedly being unpatentable over Lucas *et al.* and/or Dasch *et al.* in view of Marks, and Iwata *et al.* for the reasons set out in Paper Nos. 15, 18, 22, 26 and 36 as further evidenced by Englemen or Queen *et al.*

By way of summary, the Examiner maintained that Engleman *et al.*, Kaluga, et al., or Queen *et al.*, despite the fact that they only teach humanized antibodies to TGFβ, provide "clear motivation for the use of anti-human TGFβ for a variety of procedures."

The Examiner also stated:

> ". . . it was readily apparent to the ordinary artisan at the time the invention was made to provide antibodies that were as human as possible to decrease their immunogeneity for therapeutic procedures. This is the very reason that nine antibodies were humanized. Clearly, it would have been apparent to the ordinary artisan at the time the invention was made to generate antibodies that were as human as possible hence human antibodies to antigens of interest."

[see Paper 46, page 6]

The Examiner states further that:

> ". . . Marks *et al.* does state that the phage display library can be used to isolate human antibodies against any antigen by passing hydrogen [sic] technology and immunization."

Despite the Declaration testimony of Dr. Bruce L. Roberts to the contrary, attached hereto as Exhibit A and which was filed during the prosecution of the 08/571,755 application, the Examiner concluded that the

> ". . . applicant has not provided objective evidence that given the teachings of Marks *et al.*, which does teach making antibodies to human antigens; the ordinary artisan would not have had a reasonable expectation of success at the time the invention was made."

In discussing Dr. Robert's declaration, the Examiner has imbued Marks *et al.* with an authority far beyond the reasonable inferences that one skilled in the art would be reasonably expected to draw therefrom, (See *In re Preda*, 401 F.2d 825, 159 U.S.P.Q. 342, 344 (CCPA 1968), (see also MPEP § 2144.01) particularly in view of the well-known knowledge in the art relating to the phenomenon of immune tolerance.

Immune tolerance refers to the fact that humans do not, under most circumstances, make antibodies against self-antigens. In fact, humans have evolved several mechanisms by which to actively eliminate or inactivate auto-reactive B cell clones expressing genes encoding anti-self antibodies.

Among the mechanisms of immune tolerance that eliminate autoreactive B cells are "clonal deletion" whereby B cells arising in the bone marrow that bind to self antigen with high avidity are deleted via, for example, by apoptosis (see, *e.g.*, Roitt *Essential Immunology* p129-133 Blackwell (1989), Kuo *et al.*, *Molec. Immunology*, 36:471-479 (1999), attached as Exhibits B & C respectively). Another mechanism, referred to as "receptor editing" helps regulate autoreactive B

cells whereby the immunoglobulin genes in autoreactive B cells undergo further rearrangement to generate non-autoreactive specificities (Kuo, *et al.*, 1999). Still another mechanism of immune tolerance is known as "anergy" whereby B cells may have genes encoding antibodies to self antigens are rendered unresponsive in that they cannot proliferate and cannot produce antibodies.

Further, it is believed that genes encoding antibodies have evolved toward those that recognize foreign antigens and away from those that recognize self antigens.

In view of the well-known phenomenon of tolerance which strongly mitigates against the ability to isolate human antibodies to human self antigens, the Applicants submit that the scant disclosure of Marks is insufficient to overcome the weight of this prejudice and thus does not provide the requisite expectation of success necessary to render the present invention obvious either alone or in combination with any of the cited references.

In view of the foregoing, the Applicant submits that the subject matter of claims 1-5 and 10-12 (formerly claims 49, 51-54) is not obvious over the cited art.

III. The Obviousness-Type Double Patent Rejections of the Patent Application Are Moot

Parent application serial nos. 09/054,847 and 08/571,755 were rejected over each other under the doctrine of obviousness-type double patenting.

The Applicant submits that these rejections are moot in view of the fact that both applications were combined into the present application and acknowledgment thereof is requested.

IV. Statement in Compliance With 37 CFR § 1.56 Regarding Ownership and Date of Invention

As discussed above, the present application is the result of combining U.S. application nos. 09/054,847 and 08/571,755.

The following chart sets out ownership and inventors of each of the predecessor applications,

Application No. 10/625,307
Filed: July 23, 2003

Docket No. 05569.0007.CPUS02

Application No. 08/571,755 Assignee: Cambridge Antibody Technology Limited/Medical Research Council)	Application No. 09/054,847 Assignee: Cambridge Antibody Technology Limited
Julia Elizabeth Thompson	Julia Elizabeth Thompson
Tristan John Vaughan	Tristan John Vaughan
Andrew James Williams	Andrew James Williams
Jonathan Alexander Green	Jonathan Alexander Green
Ronald Henry Jackson	Ronald Henry Jackson
Louise Bacon	Louise Bacon
Kevin Stuart Johnson	Kevin Stuart Johnson
Raymond Paul Field	Alison Ronald Wilton
Alison Jane Wilton	Philip Ronald Tempest
Philip Ronald Tempest	Anthony Richard Pope
Stephen Paul Ruddick	
Gregory Paul Winter	

Claims 24-37 of the present application correspond to claims 16-33 of the 09/054,847 application and constructively reduced to practice as of April 3, 1998, the U.S. filing date of the 09/054,847 application, which claims priority from PCT/GB96/02450, filed on 7 October 1996, and from United Kingdom application 9520486.3, filed on 6 October 1995, 9601081.4, filed 19 January 1996 as well as U.S. Patent No. 5,885,793, filed 1 June 1994.

Claims 1-23 of the present application correspond to claims 1-23 of the 08/571,755 application and were constructively reduced to practice at least as early as of December 13, 1995, the U.S. filing date of the 08/571,755 application. The application also claims priority from U.S. application Nos. 08/244,597, filed 1 June 1994, now U.S. Patent No. 5,885,793, and 08/350,260, filed 5 December 1994, now U.S. Patent No. 5,962,255, and PCT/GB92/02240 filed 2 December 1992, which issued patents are listed in accompanying Form PTO SB08A.

Application No. 10/625,307
Filed: July 23, 2003

Docket No. 05569.0007.CPUS02

Conclusion

For the reasons discussed above, the applicants submit that the present application is in condition for allowance and early notification therefore is earnestly solicited.

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